Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	Medtronic PERIcardial SurGical AOrtic Valve ReplacemeNt Pivotal Trial (PERIGON)
Clinical Investigation Plan Identifier	DOCUMENT #10099766DOC IDE# G140056
Clinical Investigation Plan Version	1F
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Sponsor/Local Sponsor	Medtronic, Inc. Cardiac Surgery Clinical Research & Medical Science8200 Coral Sea Street N.E. MVS66 Mounds View, MN 55112 USA Medtronic Bakken Research Centre BV CardioVascular Department, Coronary and Structural Heart Disease Endepolsdomein 5 6229 GW Maastricht, The Netherlands Medtronic of Canada Ltd. 99 Hereford St. Brampton, ON L6Y 0R3, Canada

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Initial Release	Cathy Zeng
2.0	Revision to clarify the intent of the interim analysis as supplementary information	Cathy Zeng
3.0	To align SAP with CIP version 1D	Cathy Zeng
4.0	To align SAP with CIP version 1E: • Sample size increase to 1300 • Add clarifying detail of interim analysis method	Cathy Zeng
5.0	Add submission strategy for 17mm and 29mm, clarify endpoint for interim analysis, and poolability analysis for geographies.	Cathy Zeng
6.0	Update KM confidence interval method	Cathy Zeng
7.0	Updated based on SAP template version C. • Add section 2 for List of Abbreviations and Definitions of Terms • Add section 5 for investigation section including study duration, inclusion/exclusion criteria • Add 7.1.1 Disposition of Subjects • Add 7.1.2 Clinical Investigation Plan (CIP) Deviations • Add 7.5 adjustments for multiple comparisons • Add 7.7 Treatment Characteristics • Add 7.10 safety evaluation • Add 7.11 Changes to Planned Analysis • Add 8 Validation Requirements Updated SAP to reflect PERIGON pivotal trial CIP 1F Add TAV-in-SAV analysis population in the analysis set section in 7.1.3	Fang Liu, Principal Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
AVR	Aortic Valve Replacement
CABG	Coronary Artery Bypass Graft
CIP	Clinical Investigation Plan
EOA	Effective Orifice Area
EOAI	Effective Orifice Area Index
GFR	Glomerular Filtration Rate
HOCM	Hypertrophic Obstructive Cardiomyopathy
LAA	Left Atrial Appendage
OPC	Objective Performance Criteria
PFO	Patent Foramen Ovale
PMA	Pre-market Approval Application
PVL	Paravalvular Leak
SAP	Statistical Analysis Plan
TAV in SAV	Transcatheter aortic valve implantation for a failing surgical bioprosthesis

3. Introduction

PERIGON Pivotal Trial is a prospective, interventional, non-randomized, worldwide, multi-site trial, with each center following a common protocol. The purpose of this trial is to evaluate the safety and efficacy of the Medtronic Model 400 bovine pericardial stented aortic bioprosthesis in a patient population undergoing surgical aortic valve replacement. All enrolled subjects will be assigned to aortic surgical valve replacement with the Model 400 Aortic Valve Bioprosthesis. The trial design is based on the recommendations of the FDA Heart Valve guidance document (2010) and EN ISO 5840:2009 standard for cardiac valve prostheses. This Statistical Analysis Plan (SAP) is designed to document, before data are analyzed, the rationale for the design of the study and the planned analyses that will be included in study reports, based on PERIGON Pivotal Trial Clinical Investigation Plan (CIP) version specified on the SAP cover page. This SAP does not limit the analysis in reports. Additional analysis of the trial data beyond this plan is expected.

4. Study Objectives

Safety objective: to evaluate the safety of the Model 400 valve with respect to valve-related adverse events and death

Effectiveness objective: to confirm the effectiveness of the Model 400 valve with regard to NYHA classification and hemodynamic performance.

4.1 Safety Objective

The safety objective is to evaluate the safety of the Model 400 valve with regard to valve-related adverse events and death.

4.1.1 Endpoints

Safety of the valve will be evaluated by the time-related incidence of valve-related adverse events and death. The following valve-related adverse events will be evaluated in this trial: Thromboembolism, Thrombosis, Hemorrhage, Paravalvular leak (PVL), Endocarditis, Hemolysis, Structural valve deterioration, Non-structural dysfunction, Reintervention, Explant, and Death.

4.2 Effectiveness Objective

The effectiveness objective is to confirm the effectiveness of the Model 400 valve, with regard to NYHA Functional Classification and hemodynamic performance.

4.2.1 Endpoints

The effectiveness endpoints are

- NYHA Functional Classification (at discharge (or 30 days), 3-6 months, 1 year and annually thereafter through 5 years) is a classification system for defining cardiac disease and related functional limitations into four broad categorizations:

Class I	Subject with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

- Hemodynamic Performance (at discharge (or 30 days), 3-6 months, 1 year and annually thereafter through 5 years) including
  - effective orifice area (EOA)
  - effective orifice area index (EOAI)
  - peak pressure gradient
  - mean pressure gradient

- valvular regurgitation
- performance index
- cardiac output
- cardiac index

5. Investigation Plan

A maximum of 1300 subjects will be implanted at up to 40 sites with approximately 14 sites in Europe, 4 in Canada and up to 22 in the United States. Each implanted subject will be consented to be followed for 5 years, or until trial closure. A minimum follow-up of both 150 patients followed to 1-year and 400 patient-years will be completed to satisfy the requirements stated in EN ISO 5840:2009. A minimum follow-up of both 300 patients followed to 1-year and 800 patient-years will be completed to satisfy the requirements stated in the FDA Heart Valve Guidance. Total expected duration of the trial is approximately 8 years.

Patients who require aortic valve replacement (AVR) for any reason may be considered for this trial if they meet all of the inclusion and none of the exclusion criteria.

5.1 Inclusion Criteria

Patients must meet all of the following criteria to be included in the trial.

1. Patient has moderate or greater aortic stenosis or regurgitation, and there is clinical indication for replacement of their native or prosthetic aortic valve with a bioprosthesis, with or without concomitant procedures, which are limited to any of the following:
   - LAA ligation
   - CABG
   - PFO closure
   - Ascending aortic aneurysm or dissection repair not requiring circulatory arrest
   - Resection of a sub-aortic membrane not requiring myectomy
2. Patient is geographically stable and willing to return to the implanting site for all follow-up visits
3. Patient is of legal age to provide informed consent in the country where they enroll in the trial
4. Patient has been adequately informed of risks and requirements of the trial and is willing and able to provide informed consent for participation in the clinical trial

5.2 Exclusion Criteria

1. Patients who meet any of the following criteria will not qualify for participation in the trial. Patient has a pre-existing prosthetic valve or annuloplasty device in another position or requires replacement or repair of the mitral, pulmonary or tricuspid valve
2. Patient has had previous implant and then explant of the Model 400 aortic valve bioprosthesis
3. Patient presents with active endocarditis, active myocarditis, or other systemic infection

4. Patient has an anatomical abnormality which would increase surgical risk of morbidity or mortality, including:
   - Ascending aortic aneurysm or dissection repair requiring circulatory arrest
   - Acute Type A aortic dissection
   - Ventricular aneurysm
   - Porcelain aorta
   - Hostile mediastinum
   - Hypertrophic obstructive cardiomyopathy (HOCM)
   - Documented pulmonary hypertension (systolic >60mmHg)
5. Patient has a non-cardiac major or progressive disease, with a life expectancy of less than 2 years. These conditions include, but are not limited to:
   - Child-Pugh Class C liver disease
   - Terminal cancer
   - End-stage lung disease
6. Patient has renal failure, defined as dialysis therapy or GFR<30 mL/min/1.73 m2.
7. Patient has hyperparathyroidism
8. Patient is participating in another investigational device or drug trial or observational competitive study
9. Patient is pregnant, lactating, or planning to become pregnant during the trial period
10. Patient has a documented history of substance (drug or alcohol) abuse
11. Patient has greater than mild mitral valve regurgitation or greater than mild tricuspid valve regurgitation as assessed by echocardiography
12. Patient has systolic EF<20% as assessed by echocardiography
13. Patient has Grade IV Diastolic Dysfunction
14. Patient has documented bleeding diatheses
15. Patient has had an acute preoperative neurological deficit or myocardial infarction and has not returned to baseline or stabilized ≥30 days prior to enrollment
16. Patient requires emergency surgery

6. Determination of Sample Size

Sample size for this trial was based on the safety objective. Sample size calculations were not performed for the effectiveness objective.

6.1 Sample Size Methods and Assumptions

Table 1: OPC for Tissue Prosthetic Heart Valves

Adverse Event	*Linearized Rate (% per Patient-year)*
Thromboembolism	2.5
Valve Thrombosis	0.2

All Hemorrhage	1.4
Major Hemorrhage	0.9
All Paravalvular Leak	1.2
Major Paravalvular Leak	0.6
Endocarditis	1.2

The safety objective will be assessed by comparing linearized valve-related adverse event rates from subjects implanted with the Model 400 valve to acceptable linearized valve-related adverse event rates following valve replacement as defined by FDA in the Heart Valve Guidance 2010[i] and EN ISO 5840:2009[ii] as Objective Performance Criteria (OPC). The OPC for tissue valves (based on the linearized rate) are presented in Table 1.

Sample size estimation is based on the methods of Grunkemeier [iii]. The following are assumptions for the sample size estimate:

One-sided alpha = 0.05

Power = 1- β = 80%

$2XR_{\_OPC}$ = 2.4%

$R_{\_Model400}$= 1.2%

In the above expressions, $2XR_{\_OPC}$ and $R_{\_Model400}$ denote the Performance Goal (null hypothesis proportion) and true proportion, respectively.

If the endpoint event has a constant risk of $R_{\_OPC}$ per patient-year, then the distribution of the number of endpoint events occurring during a fixed time of T patient-years is a random variable E with Poisson distribution of mean $\lambda = R_{\_OPC} \times T$. Thus, the probability of observing n or fewer events during T patient-years is:

$$P_\lambda(E \le n) = \sum_{k=0}^{n} e^{-\lambda} \frac{\lambda^k}{k!}$$

To reject the null hypothesis of $R_{\_Model400} \ge 2 \times R_{\_OPC}$, the number of events E occurring during T patient-years is less than or equal to the critical value of n_{cv}. The critical value of n_{cv} is determined by the selected Type I (α) and Type II (β) levels. That is:

$$\begin{cases} P_{2\lambda}(E \le n_{cv}) \le \alpha \\ P_\lambda(E \le n_{cv}) \ge 1 - \beta \end{cases}$$

Thus the amount of data required to test the null hypothesis using the acceptable adverse event rate of 1.2% per patient-year is approximately 800 patient-years using the Poisson distribution, an alpha level of 5% and at least 80% power.

If all subjects are enrolled within a one-year time frame, and followed for one year postoperatively, then a total of 556 implants are required, considering a 5% attrition rate (Grunkemeier 1994). Therefore, accounting for attrition and expected enrollment rates, up to 650 implants are expected to gain 800 patient-years. With CIP version specified on SAP cover page, up to 1300 subjects will be implanted to allow for continuing enrollment during the regulatory submission to commercialization time period, to avoid a significant interruption in access to surgeons of the latest surgical valve technology.

6.2 Rationale for Choice of Hypothesis

As the OPC presented in Table 1, Valve Thrombosis, Major Hemorrhage and Major PVL rate are all less than 1.2% per patient-year, and to achieve the 80% power for these tests, a much larger sample size is required to evaluate these rare events. For example, to detect a Major Paravalvular Leak rate of 0.6% per patient-year, more than 1800 patient-years of data are required; and to detect a Valve Thrombosis rate of 0.2% per patient-year, more than 5000 patient-years of data are required. Such a large sample size requirement may leave the trial un-executable. Thus, the smallest acceptable adverse event rate of 1.2% per patient-year (excluding Valve Thrombosis, Major Hemorrhage and Major PVL) is chosen for the sample size assumption.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subjects disposition will be summarized, including the number of subjects enrolled/implanted, died, explanted, withdrawn, lost-to follow up, and completed each visit during the study.

7.1.2 Clinical Investigation Plan (CIP) Deviations

A protocol deviation is defined as an event within a study that did not occur according to the CIP or Clinical Trial Agreement. Protocol deviations will be reported regardless of whether they are pre-approved by Medtronic. Deviations will be summarized by type for each interval. The percent of subjects with the deviations will be calculated based on the number of subjects eligible for the specified visit.

7.1.3 Analysis Sets

The primary analysis will be performed on the implanted population (as treated population). The implanted population consists of all enrolled subjects who are actually implanted with the Model 400 valve. To be considered implanted, the subject's device disposition form must show at least one device with a final disposition of "Implanted." Time zero begins at the date of the procedure.

The data from the subjects with attempted procedures, but who were not implanted with the Model 400 valve will be summarized separately and reported as descriptive statistics. The subjects with attempted procedures will not be counted towards the total number of implants.

The subjects with TAV in SAV procedures are identified as TAV-in-SAV population. The TAV in SAV population includes all patients who had Implantation of transcatheter valve within Model 400 Valve (valve in valve) from valve reintervention eCRF. The hemodynamic results after explant or TAV-in-SAV procedures won't be included in the hemodynamic tables for the main cohort. A separate analysis for TAV-in-SAV cohort will be created on an ad-hoc basis.

7.2 General Methodology

7.2.1 Reports for which this Statistical Analysis Plan Applies

This SAP applies to the trial report for Pre-market Approval Application (PMA) to the Food and Drug Administration (FDA) and the final report.

This SAP applies to the trial report for CE mark submission and to the report for regulatory submissions in other geographies.

The analyses for CE mark approval and FDA approval may be used for regulatory submissions in other geographies.

This SAP applies to the main trial manuscript, though the manuscript may not include all analyses specified in this document.

7.2.2 Special Considerations

7.2.2.1 Report Timing and Cutoff Dates

Cutoff dates will be applied to all site case report forms. A Visit Cutoff Date and a Received Cutoff Date will be used. The visit cutoff date will be the first date on which at least 800 patient-years of data have been collected for the PMA report. The visit, assessment, and event dates will be used to determine which case report forms satisfy the visit cutoff date. The received cutoff date will be determined near the time of the database closure and will be chosen to ensure that all forms of critical importance have been received while still allowing adequate time for data cleaning between the received cutoff date and the date of database closure. The "logints" log-in timestamp field will be used to determine which case report forms satisfy the received cutoff date. CE mark report Visit Cutoff Date and a Received Cutoff Date will be used similarly when regulatory submission data requirement is met.

Any forms which do not have a visit date directly on the form will use the visit date from the corresponding form for that entry. Forms with multiple dates will apply cutoff dates to individual lines of data on the form.

7.2.2.2 Definition of Enrolled Subject

An enrolled subject is defined as a subject whose IRB/MEC-approved patient informed consent form has been signed and dated by all required parties.

7.2.2.3 P-Values

The statistical test for the safety objective will be performed at one-sided α=0.05. All reported p-values greater than or equal to 0.0001 will be rounded to four decimal places. P-values less than 0.0001 will be displayed as "<0.0001."

7.2.2.4 Kaplan-Meier Analyses

Kaplan-Meier analysis of event-free rates (or event rates) will be performed at 30 days, 6 months, 12 months and annually through five years. These times correspond to 30 days, 180 days, 365 days, 730 days, 1095 days, 1460 days, and 1825 days, respectively. At each time point with data, the product-limit estimate of the event-free rate (or event rate), the number of subjects at risk, the number of

subjects with events, the number of subjects censored, and the loglog transformed 95% confidence interval using the Greenwood standard error will be presented.

For subjects without an event, the date of censoring will be the latest date of all follow-up visits, assessments, and events (including death).

7.2.2.5 17 mm and 29 mm Valves

If at the time of PMA and CE mark submissions, PERIGON Pivotal trial does not have fifteen 17mm subjects successfully implanted with Model 400 valve and followed for at least one year, 17mm study data from PERIGON Japan Trial will be utilized to support 17mm market approval in United States and other global geographies.

The PERIGON Japan Trial with 17mm valve is a prospective, interventional, non- randomized, multi-site trial to evaluate the safety and effectiveness of the 17mm aortic bioprosthesis in a patient population undergoing surgical aortic valve replacement with the similar inclusion and exclusion criteria as the PERIGON Pivotal trial.

Similarly for 29 mm valve, if at the time of PMA and CE mark submission, PERIGON Pivotal trial does not have fifteen 29 mm subjects successfully implanted with Model 400 valve and followed for at least one year, the enrollment may continue for 29 mm subjects until the regulatory requirement is met.

7.2.2.6 Data Safety Monitoring Board (DSMB)

A DSMB will be established to review accumulating data from the trial, advise Medtronic on the continuing safety of current and future trial participants, and the continuing validity and scientific merit of the trial.

Additional details about the DSMB are outlined in the DSMB charter.

7.3 Center Pooling

Geographies will be United States, Canada and European. Sites that successfully implanted less than 5 subjects will be considered “small sites” and will be pooled together as one site.

The evaluation of the effect of sites and geographies over time to valve-related adverse events and death will be performed as follows:

Cox Proportional Hazards model will be used to evaluate the site and geographies effect on valve-related adverse events. If the resulting p-value for site is > 0.15, the data will be considered to be poolable across trial sites and geographies. Otherwise, if the resulting p-value for site is $\leqslant$ 0.15, further exploratory analysis will attempt to identify covariates that may explain possible heterogeneity among the sites and geographies. All other possible clinically meaningful baseline risk factors then will also be included in the above model as independent variables. A backwards elimination process will be utilized to pare the model down. In this process, the single-term baseline variable with the highest p-value will be removed from the model (except sites and geographies) until all factors have a p-value less than 0.15.

The possible clinically meaningful baseline risk factors include age at implant, gender, preoperative NYHA classification, previous aortic valve replacement, valve size, and concomitant CABG.

If this multivariate model does result in p-value of site > 0.15 after adjustment for these baseline factors, then outcome results will again be considered poolable across trial sites. If the resulting p-value for site is still $\leqslant$ 0.15 after adjustment for these factors, results will be presented by investigational center and the clinical significance of these differences will be assessed.

Any observation with missing values for the response or explanatory variables will be excluded from the analysis.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

Every effort will be undertaken to minimize missing data. In time-to-event outcomes, dropouts will be censored at the time of discontinuation, consistent with the Kaplan-Meier approach. Unless specified otherwise in each objective, no statistical techniques will be used to impute missing data. If a subject's data are missing for any reason, that subject will not be included in that portion of the analysis. The number of subjects included in each analysis will be reported so that the potential impact of missing data can be assessed.

In the case of partial dates, the general rule is as follows:

- If only the month and year are known, the event or assessment will be analyzed as if it occurred on the 15th of that month.
- If only the year is known, the event or assessment will be analyzed as if it occurred on June 30th of that year.

These resolutions of partial dates are subject to the restrictions that pre-procedure events and assessments must occur between the enrollment date and the procedure date, and post-procedure events and assessments must occur no earlier than the procedure date. If additional information about the partial dates might be known, for example, the event occurs after 15th of the month, then data may be analyzed as if it occurred on the 16th of the month.

7.5 Adjustments for Multiple Comparisons

There are no planned multiple comparisons expected and thus no multiplicity adjustments are planned for this study.

7.6 Demographic and Other Baseline Characteristics

Major baseline demographic and clinical variables will be summarized for the enrolled and implanted populations. All continuous variables will be summarized with means, standard deviations, medians, interquartile ranges, minimums, and maximums. Categorical variables will be summarized with frequencies and percentages.

7.7 Treatment Characteristics

Implant procedure data will be summarized for the implanted populations. All continuous variables will be summarized with means, standard deviations, medians, interquartile ranges, minimums, and maximums. Categorical variables will be summarized with frequencies and percentages.

7.8 Interim Analyses

Interim analysis is planned when at least 200 patient-years of data are collected. However, there are no plans for early termination of the trial due to superiority or futility of the investigational therapy based on the interim results.

An interim analysis of the trial data is planned to evaluate the early safety profile of the Model 400 valve. The interim analysis may be included as supplementary information in a submission for CE Mark and may be used for regulatory submissions in other geographies.

7.8.1 Safety Objective

The safety objective is to evaluate the safety of the Model 400 valve with regard to valve-related adverse events and death.

7.8.1.1 Endpoints

Safety of the valve will be evaluated by the time-related incidence of valve-related adverse events with OPC. The following valve-related adverse events will be evaluated in this analysis: Thromboembolism, Thrombosis, Major Paravalvular leak, Endocarditis.

7.8.1.2 Hypothesis

The safety objective will be assessed by comparing a composite linearized adverse event rate from subjects implanted with the Model 400 valve to twice the composite linearized adverse event rate of valve-related Thromboembolism, Endocarditis, Major PVL and Thrombosis. The composite rate was developed using individual valve-related event rates from the Objective Performance Criteria (OPC) as defined by FDA Heart Valve Guidance 2010[vi] and EN ISO 5840:2009ii From Table 1, twice the composite linearized adverse event rate of Thromboembolism, Endocarditis, Major PVL and Thrombosis is 2 X (2.5 + 0.2 + 0.6 + 1.2) = 9% per patient year.

The interim analysis hypothesis is to test that the true composite linearized adverse event rate of Thromboembolism, Endocarditis, Major PVL and Thrombosis for the Model 400 valve ($P\_{Model400}$) is equal to or greater than twice the composite linearized adverse event rate of commercially available tissue prosthesis valves.

The null (H_0) and alternative (H_A) hypotheses are written as follows:

H_0: $P\_{Model400} \geq 9\%$

H_A: $P\_{Model400} < 9\%$

Where $P\_{Model400}$ is the composite linearized adverse event rate for the Model 400 valve.

7.8.1.3 Sample Size Methods and Assumption

7.8.1.3.1 Sample Size Methods and Assumptions

The objective will be evaluated with a fixed sample size group sequential design with one interim analysis at 200 patient-years and one possible second analysis at 400 patient-years.

A fixed sample size group sequential design with O'Brien-Fleming boundaries for one interim analysis will be utilized. A fixed sample size design of 400 patient-years with one interim analysis at 200 patient-years achieves at least 90% power. The assumptions for sample size / power calculation:

- P_Baseline (the baseline rate: observed in the literature) = 3.5%
- P_ Model400 (the assumed rate for Model 400) = 3.5%
- Type I error (α) =0.05
- One interim analysis at 200 patient-years

7.8.1.3.2 Rationale for Choice of Hypothesis

The composite rate and hypothesis were chosen because it provides an overall evaluation of safety of the device by incorporating significant device-related events that are clinically relevant to evaluating a new bioprosthetic heart valve.

7.8.1.4 Data Collection and Analysis Method

There will be up to two analyses of this objective. The first analysis may occur when 200 patient-years of data are collected, and the second analysis may occur when 400 patient-years of data are collected. Spending function with boundaries similar to that for O'Brien-Fleming[vii] will be used to control the Type I and Type II error probabilities. The table below illustrates the O'Brien-Fleming boundaries and the associated z-statistic and p-value for each analysis under an assumption that 200 patient-years of data are observed at the interim analysis. However, if the observed patient-years of data are different at the time of the interim analysis, the boundaries and p-values will be recalculated to reflect the appropriate percentage of the total sample size observed at the time of the interim analysis.

Table 2: O'Brien-Fleming boundary at the interim and 400 patient-year analysis

Analysis	Z-statistic	P-value
Interim	-2.3585, 0.0000	0.0092, 0.5000
400 patient-years	-1.6677	0.0477

*S-Plus 8.2/S+ SeqTrial used with the O'Brien-Fleming Type I error spending function.

The above sample rate boundaries are also shown in Figure 1:

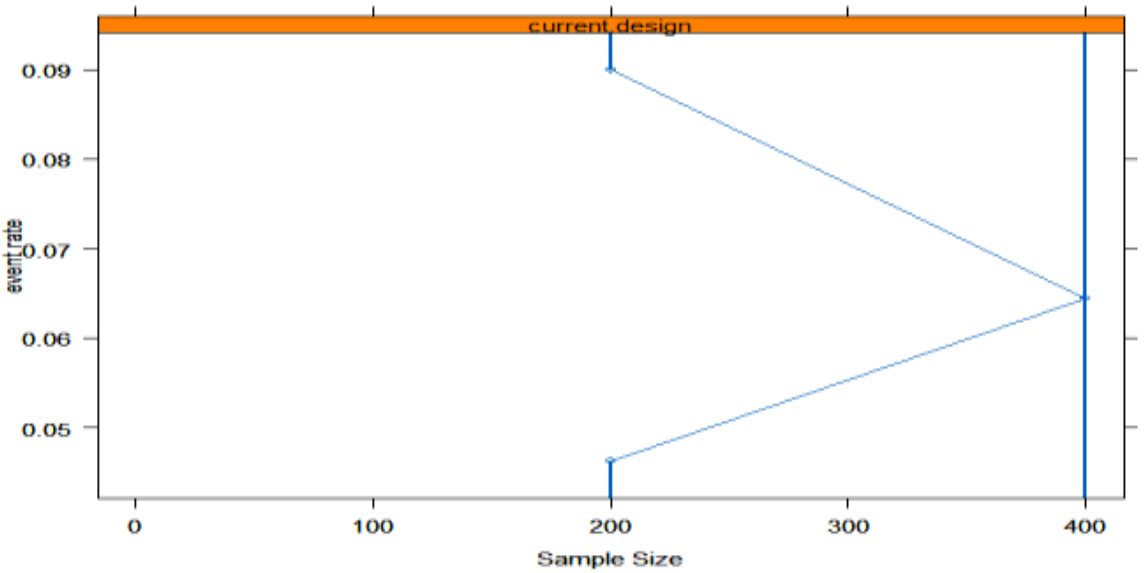

Figure 1: Event Rate boundaries using O'Brien-Fleming Method

Since there may be up to two analyses, there are two thresholds for which the observed test statistic will be evaluated. Call this set of thresholds $Z_t = (Z_1, Z_2)$. Each of these thresholds will be a standard normal Z statistic evaluated at the nominal alpha level for the analysis. For example, in the table above, the nominal alpha level for the interim analysis is 0.0092 with an associated Z statistic of -2.3585. Thus, if the Z statistic is smaller than -2.3585, the null hypothesis may be rejected at the interim analysis. Similarly, if the null hypothesis cannot be rejected at the interim analysis, the null hypothesis may be rejected at the 400 patient-years analysis provided the Z statistic is smaller than -1.6677. To reject the null hypothesis demonstrates statistically that the Model 400 valve composite adverse event rate is less than 9%. This method preserves the Type I error rate at 5% since the conservative O'Brien-Fleming rules are utilized in setting the rejection thresholds Z_t.

- At the interim analysis (200 patient-years), if the data support the alternative hypothesis that the Model 400 valve composite rate is <9%, the results will be summarized and submitted as applicable as described in section 7.8. The 400 patient-year analysis will not be performed under this scenario.
- If the criteria are not met at the 200 patient-year interim analysis, the trial will continue to gather data to at least 400 patient-years and then summarize the data and submit as applicable as described in section 7.8.

In both scenarios, the trial conduct will not be altered, and the trial will not stop, but continue until at least 800 patient-years of data are collected.

Z test will be carried out to assess statistical significance, and the test statistic will be calculated as:

$$z = \frac{p - \pi_0}{\sqrt{\pi_0 / n}}$$

In the above expression π_0=9% per patient-year, the Performance Goal, p is the late linearized rate of the composite events, which is calculated as number of late events divided by late patient-years, and n is late patient-years. The test is one-sided and the resulting p-value will be compared to the interim O'Brien-Fleming p-value.

Each component of the composite adverse event rate will also be summarized and described. Kaplan-Meier survival analyses will also be performed to summarize the adverse event data.

7.8.2 Effectiveness Objective

The effectiveness objective is to confirm the effectiveness of the Model 400 valve regarding the NYHA Functional Classification and hemodynamic performance.

7.8.2.1 Endpoints

The effectiveness endpoints are:

- NYHA Functional Classification (at discharge or within 30 days, 3-6 months, 1 year and annually thereafter through 5 years)
- Hemodynamic Performance (at discharge or within 30 days, 3-6 months, 1 year and annually thereafter through 5 years) including
    - effective orifice area (EOA)
    - effective orifice area index (EOAI)
    - peak pressure gradient
    - mean pressure gradient
    - valvular regurgitation
    - performance index
    - cardiac output
    - cardiac index

7.8.2.2 Hypothesis

No formal hypothesis will be evaluated for this objective. Control articles based on current literature of previously approved heart valves will be selected. Data from the control articles will be provided so as to inform the reader of the current state of heart valve technology, as expressed by articles in quality peer-reviewed journals, and to allow for evaluation of the Model 400 data.

7.8.2.3 Sample Size Methods and Assumptions

Sample size calculations were not performed for the effectiveness objective. Sample size for the interim analysis was based on the safety objective.

7.8.2.4 Data Collection and Analysis Methods

NYHA functional classification and echocardiographic hemodynamic data will be summarized using descriptive statistics for continuous variables and frequency tables for discrete variables.

For NYHA, a frequency table will be presented for each visit interval to show how many subjects fall into each of the four categories of NYHA functional classification. For each subject with paired data, the number of classes changed from baseline will be calculated at discharge (or 30 days), 3-6 months, 1 year and annually thereafter through 5 years and summarized into categories as Improved, No Change and Worsened.

All echocardiograms will be analyzed by an echo core lab which will determine the values for the Hemodynamic Performance endpoints. Valvular regurgitation will be summarized with a frequency table for each visit interval and the other Hemodynamic Performance endpoints will be summarized as with continuous data. For each subject with paired data, the change from baseline may also be calculated at discharge (or 30 days), 3-6 months, 1 year and annually thereafter through 5 years. These data will be summarized by valve size.

Control articles based on current literature of previously approved heart valves will be selected. Effectiveness data from the control articles will be provided so as to inform the reader of the current state of heart valve technology, as expressed by articles in quality peer-reviewed journals, to allow for evaluation of the Model 400 valve effectiveness data.

7.9 Evaluation of Objectives

7.9.1 Safety Objective

The safety objective is to evaluate the safety of the Model 400 valve with regard to valve-related adverse events and death.

7.9.1.1 Endpoints

Safety of the valve will be evaluated by the time-related incidence of valve-related adverse events and death. The following valve-related adverse events will be evaluated in this trial: Thromboembolism, Thrombosis, Hemorrhage, Paravalvular leak (PVL), Endocarditis, Hemolysis, Structural valve deterioration, Non-structural dysfunction, Reintervention, Explant, and Death.

7.9.1.2 Hypothesis

The safety objective will be assessed by comparing linearized valve-related adverse event rates from subjects implanted with the Model 400 valve to acceptable linearized valve-related adverse event rates following valve replacement as defined by FDA in the Heart Valve Guidance 2010[i] and EN ISO 5840:2009[ii] as Objective Performance Criteria (OPC). The OPC for tissue valves (based on the linearized rate) are presented in Table 1.

The trial is designed to test the hypothesis that the true linearized adverse event rate for the Model 400 valve ($R\_{Model400}$) is equal to or greater than twice the acceptable rate of commercially available tissue prosthetic valves (R_{OPC}). The null (H_0) and alternative (H_A) hypotheses are written as follows.

$$H_0: R\_{Model400} \geq 2 \times R\_{OPC}$$

$$H_A: R\_{Model400} < 2 \times R\_{OPC}$$

Where $R_{Model400}$ is the linearized adverse event rate for the Model 400 valve and R_{OPC} is the acceptable rate of commercially available tissue prosthetic valves. To reject the null hypothesis demonstrates statistically that the rate for the Model 400 valve is less than two times the acceptable rate.

7.9.1.3 Data Collection and Analysis Methods

7.9.1.3.1 Data Collection and Analysis

Adverse device effects and outcomes will be identified and reported by the Investigator at all visits. All deaths and endpoint related adverse events will be reviewed by the CEC.

Early postoperative events are defined as those occurring on or before 30 days post-operative. Late postoperative events are those occurring after 30 days post-operative.

Early rates of adverse events will be calculated as the number of early adverse events divided by the total number of subjects, expressed as a percentage.

The late events rates will be calculated using the linearized event rate methodology. That is, the rate will be the number of late events divided by the late post-operative patient-years. For those adverse events with OPC available, the linearized rates and their associated one-sided upper 95% confidence bounds will be compared to the Objective Performance Criteria (OPC) to show that they are within acceptable limits. Formally, the method introduced by Cox[iv] which gives the relatively most accurate results[v] will be used:

$$\chi_{.95,2n_e+1}/2\mathrm{Y_T}$$

where ne is the number of late events and YT is the late post-operative patient-years. If there is 0 events, the one-sided upper 95% confidence bound will be 0.

Kaplan-Meier survival analyses will also be performed to summarize valve-related adverse events and death. The Kaplan-Meier rate and the corresponding 95% confidence interval will be presented for each visit interval. In addition, number of subjects at risk, number of events, number of censored subjects and the Kaplan-Meier survival curve or event curve will also be displayed.

In addition, control articles based on current literature of previously approved heart valves will be selected. Adverse event data from the control articles will be provided so as to inform the reader of the current state of heart valve technology, as expressed by articles in quality peer-reviewed journals, and allow additional evaluation of the Model 400 adverse event data.

7.9.1.3.2 Determination of Data for Analysis

All subjects who are enrolled in the trial and have a trial valve implanted will be included for analysis.

For subjects who are attempted but not implanted, their data will be summarized separately.

7.9.2 Effectiveness Objective

The effectiveness objective is to confirm the effectiveness of the Model 400 valve, with regard to NYHA Functional Classification and hemodynamic performance.

7.9.2.1 Endpoints

The effectiveness endpoints are

- NYHA Functional Classification (at discharge (or 30 days), 3-6 months, 1 year and annually thereafter through 5 years) is a classification system for defining cardiac disease and related functional limitations into four broad categorizations:

Class I	Subject with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

- Hemodynamic Performance (at discharge (or 30 days), 3-6 months, 1 year and annually thereafter through 5 years) including
  - effective orifice area (EOA)
  - effective orifice area index (EOAI)
  - peak pressure gradient
  - mean pressure gradient
  - valvular regurgitation
  - performance index
  - cardiac output
  - cardiac index

7.9.2.2 Hypothesis

No formal hypothesis will be evaluated for this objective. Control articles based on current literature of previously approved heart valves will be selected. Data from the control articles will be provided so as to inform the reader of the current state of heart valve technology, as expressed by articles in quality peer-reviewed journals, and allow evaluation of the Model 400 data.

7.9.2.3 Data Collection and Analysis Methods

NYHA functional classification and hemodynamic data will be summarized using descriptive statistics for continuous variables and frequency tables for discrete variables.

NYHA functional class will be evaluated based on the percentage of subjects in each specific NYHA class at each postoperative time-point and the percentage of subjects at each postoperative time-point who have improved, worsened, or not changed in NYHA class compared to preoperative baseline.

All echocardiograms will be analyzed by an echo core lab which will determine the values for the Hemodynamic Performance endpoints. Valvular regurgitation will be summarized with a frequency table for each visit interval and the other Hemodynamic Performance endpoints will be summarized as with continuous data. For each subject with paired data, the change from baseline may also be calculated at discharge (or 30 days), 3-6 months, 1 year and annually thereafter through 5 years. These data will be summarized by valve size.

Control articles based on current literature of previously approved heart valves will be selected. Effectiveness data from the control articles will be provided so as to inform the reader of the current state of heart valve technology, as expressed by articles in quality peer-reviewed journals, to allow for evaluation of the Model 400 valve effectiveness data.

7.9.3 Additional Analyses

Additional analyses will be performed on the implanted population for safety and effectiveness data.

7.9.3.1 Safety Endpoints

The safety endpoints include the valve-related adverse events of Thromboembolism, PVL, reoperation, explant and all-cause mortality. Events that occurred in less than five subjects will not be evaluated by the additional analyses.

The additional safety endpoint analyses described in Section 7.9.3.1 will be included in regulatory submissions to all geographies except for Risk Factor Analysis which will be included only in the submission in US.

7.9.3.1.1 Valve Size Analysis

The evaluation of the effect of valve size over time to the valve-related adverse events and death will be performed as follows:

Cox Proportional Hazards model will be used to evaluate the valve size effect on valve-related adverse events and death.

Due to possible small sample sizes in the smallest and largest valve sizes, the 17 mm may be combined with the 19 mm and the 27 mm may be combined with the 29 mm size to create larger groups of valve sizes. Thus, four indicator variables for valve size (representing 17 mm to 19 mm, 21 mm, 23 mm, 25 mm, and 27mm to 29 mm) may be created and included in the model.

Valve size will be considered to be significantly associated with time to valve-related adverse events and death if the p-value <0.05.

7.9.3.1.2 Gender Analysis

Assessment of the possible gender differences will be examined in the freedom from (or event rate) valve-related adverse events and death after implantation of the Model 400 valve.

The possible gender differences in the event rates of death and valve-related adverse events will be evaluated using the log-rank test.

Differences in gender will be considered to be significant if the p-value<0.05.

7.9.3.1.3 Risk Factor Analysis

Risk factors associated with time to death (all causes), reoperation and explant will be evaluated using Cox Proportional Hazards model.

Variables evaluated as possible risk factors for death (all causes), valve-related reoperation and explant include age at implant, gender, preoperative NYHA classification, previous aortic valve replacement, valve size, and concomitant CABG. Other important concomitant procedures may also be included in this analysis.

A backwards elimination process will be utilized to pare the model down. In this process, the single-term baseline variable with the highest p-value will be removed from the model until all factors have a p-value less than 0.15.

7.9.3.2 Effectiveness Endpoints

The effectiveness endpoints include mean gradient, effective orifice area, valvular regurgitation and NYHA classification.

7.9.3.2.1 Valve Size Analysis

Mean gradient, effective orifice area and valvular regurgitation at one year postoperative will be summarized by valve size.

7.9.3.2.2 Gender Analysis

The NYHA classification will be summarized by gender and time intervals. The chi-squared test will be used to evaluate the possible relationship between NYHA classification and gender at different time intervals.

7.10 Safety Evaluation

An independent Clinical Events Committee (CEC) will conduct a medical review and classify/adjudicate, at a minimum, all deaths and endpoint related adverse events for seriousness and relatedness to the trial device/procedure according to definitions and processes outlined in the protocol and the CEC charter. Refer to section 7.9.1 for data collection and analysis methods of safety endpoint related adverse events. In addition, listings of all adverse events (including seriousness, treatment, and relatedness to the procedure or device), all device deficiencies, valve reintervention and explant, and all deaths will be generated.

7.11 Changes to Planned Analysis

This analysis plan is consistent with the CIP for which the plan was developed. Any deviations from the planned analysis in the CIP will be documented in an amended statistical analysis plan, when possible, and/or will be described with justification and rationale in the study report.

8. Validation Requirements

Level 1 validation (independent validation) will be used for the analysis datasets and for all hypothesis tested endpoints (co-primary endpoints and five powered secondary endpoints). Level 2 validation (peer review), at minimum, will be used for additional analyses, data summaries, and listings.

9. References

[i] FDA Heart Valve Guidance 2010.

[ii] ISO 5840:2009: Cardiovascular implants – Cardiac valve prostheses.

[iii] Grunkemeier GL, Johnson DM, and Naftel DC (1994). Sample Size Requirements for Evaluating Heart Valves with Constant Risk Events. *The Journal of Heart Valve Disease,* 1994; 3:53-58.

[iv] Cox DR (1953). Some simple approximation test for Poisson variates. *Biometrika,* 1953; 40:354- 360

[v] Grunkemeier GL, Anderson WN (1998). Clinical Evaluation and Analysis of Heart Valve Substitutes. *The Journal of Heart Valve Disease,* 1998; 7:163-169.

[vi] FDA Heart Valve Guidance 2010.

[vii] O'Brien, P. C. and Fleming, T. R. (1979). A Multiple Testing Procedure for Clinical Trials. *Biometrics*, 35, 549–556.